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**Changes to 5-HT<sub>4</sub>/5-HT<sub>3</sub> ratio subserve lower contractile response to 5-HT and greater susceptibility to 5-HT receptor desensitization in the TNBS-inflamed guinea-pig ileum**

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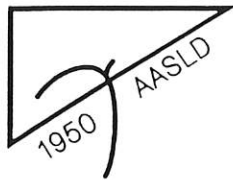
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CHANGES IN 5-HT<sub>4</sub>/5-HT<sub>3</sub> RATIO SUBSERVE LOWER CONTRACTILE RESPONSE TO 5-HT AND GREATER SUSCEPTIBILITY TO 5-HT RECEPTOR DESENSITIZATION IN THE TNBS-INFLAMED GUINEA-PIG ILEUM. J.P. Martinolle, R. Garcia-Villar, P.G. McLean, J. Fioramonti, L. Buéno. INRA, Pharmacology Dept, BP.3, 31931, Toulouse, France.

Serotonin is both a neurotransmitter, involved in the modulation of intestinal contractility, and a potent inflammatory mediator present in increased levels in inflamed tissues. The known susceptibility of 5-HT receptors to homologous desensitization, led us to investigate putative changes in the intestinal responsiveness to 5-HT receptor subtype stimulation, which could explain the altered motility associated with TNBS-induced inflammation.

**Methods:** Ileitis was induced by intrajejunal instillation of 0.3 ml TNBS in 50% ethanol (80 mg/kg); controls were given saline. Animals were sacrificed 6 days later and ileum circular muscle strips (8 x 2 mm) were mounted in an *in vitro* superfusion system (Krebs; 37°C; 2 ml/min). Isometric contractions were recorded; concentration-response curves (0.1nM-0.1mM) to serotonin (5-HT, n=12), 2-methyl-5-HT (5-HT<sub>3</sub> agonist; n=4) and 5-methoxytryptamine (5-MeOT; 5-HT<sub>4</sub> agonist; n=4) were constructed and analysed by nonlinear regression. Maximal effect (E<sub>max</sub>; mN/mm<sup>2</sup> cross-section area) and drug potency (EC<sub>50</sub>; µM) were determined (mean±SEM). 5-HT receptor desensitization was assessed in both controls (n=6) and TNBS-treated (n=6) guinea-pigs by repetitive stimulation with 10 µM 5-HT (3 min every 15 min) in presence or absence of antagonists (10 nM): ondansetron (5-HT<sub>3</sub>), DAU-6285 (5-HT<sub>4</sub>), ketanserin (5-HT<sub>2</sub>), methysergide (5-HT<sub>1-2</sub>).

**Results:** Ileum strips from both TNBS- and saline-treated animals were dose-dependently contracted by 5-HT, 2-methyl-5-HT, and 5-MeOT. The E<sub>max</sub> for 5-HT in TNBS-inflamed ileum was approx. half that observed in controls (6.9±1.8 vs 12.2±1.6 mN/mm<sup>2</sup>; p<0.05) whilst the potency was unaffected (EC<sub>50</sub>=3.2±0.7 vs 3.0±0.7 µM). The ratio of the respective 5-HT<sub>4</sub> and 5-HT<sub>3</sub> receptor-mediated responses was also lowered (approx. 25/75% of the response to 5-HT in controls vs 10/90% in TNBS-inflamed strips). 5-HT<sub>3</sub>-mediated responses to 2-methyl-5-HT were shifted to the right and 5-HT<sub>4</sub>-mediated maximal response to 5-MeOT was decreased. In desensitization experiments, the lowest response to 10µM 5-HT was 30.1±3.4% of the initial response in controls, and 11.6±2.0% (P<0.001, n=6) in TNBS strips. In both groups, desensitization was partly prevented by preincubation with ondansetron, (5-HT<sub>3</sub> antagonist) but not DAU-6285, ketanserin or methysergide.

**Conclusion:** Our results show altered 5-HT<sub>4</sub> and 5-HT<sub>3</sub>-mediated contractile responses of the intestinal circular muscle during TNBS-induced ileitis. These receptor changes subserve hyporesponsiveness to 5-HT, and a greater susceptibility of 5-HT<sub>3</sub> receptors to homologous desensitization. This later probably resulting from increased 5-HT levels, may represent a protective mechanism of the gut against subsequent stimulation during inflammation.

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